UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/585,480 | 07/31/2006 | Marc Gerspacher | 33587-US-PCT | 5896 |

75074 7590 09/03/2010

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
220 MASSACHUSETTS AVENUE
CAMBRIDGE, MA 02139

| EXAMINER | |
|---|---|
| BASQUILL, SEAN M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1613 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/03/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

NIBR.MAILDATA@NOVARTIS.COM
PATRICIA.HOFSTETTER@NOVARTIS.COM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/585,480 | GERSPACHER ET AL. | |
| | Examiner | Art Unit | |
| | Sean Basquill | 1613 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 Feb 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

1. Claims 1 and 2 have been amended, and Claims 7 and 11 cancelled. Claims 8-10 remain withdrawn as directed to nonelected inventions.

### *Previous Rejections*

2. Applicants' arguments, filed 13 May 2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. There is nothing unusual, certainly, about an examiner changing his viewpoint as to the patentability of claims as the prosecution of a case progresses, and so long as the rules of Patent Office practice are duly complied with an applicant has no legal ground for complaint because of such change in view. *In re Ruschig*, 154 USPQ 118, 120-21 (CCPA 1967). The examiner regrets extending the examination and prosecution of the instant application in this manner, but nevertheless feels the instant rejections are in keeping with the laws, regulations, and guidelines applicable to the examination of patent applications submitted to the office.

### *Claim Rejections - 35 USC § 112 First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 5, and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an actual invention, not merely an indication of a result that one might achieve if one made that invention. *See*, e.g., *In re Wilder*, 22 USPQ 369, 372-3 (Fed. Cir. 1984) (holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate'). This matter is of particular importance in the evaluation of claims drawn to a chemical genus which identifies a core compound bearing variable substituents. It has been held that "a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification...demonstrates that the applicant has invented species sufficient to support a claim to a genus" with such breadth. *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 94 USPQ2D 1161, 1171 (Fed. Cir. 2010). An adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties of species falling within the genus sufficient to distinguish the genus from other materials. *Id.*, quoting *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

However, merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species. *Ariad*, 94 USPQ2D at 1171. 35 U.S. C. 112, first paragraph, requires a description of the invention that "clearly allow[s] persons of ordinary skill in the art to recognize that the inventor *invented* what is claimed." *Ariad* at 1172, quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555 (1562-63) (Fed. Cir. 1991) (emphasis added). A sufficient disclosure is one which reasonably conveys to one having ordinary skill in the art that the inventor had possession of the claimed subject matter as of the filing date of the application in question. *Vas-Cath*, 935 F.2d at 1563. The description must reasonably describe the invention, not simply indicate a result which one might achieve if one actually made the invention. *Eli Lilly*, 119 F.3d at 1568. To properly evaluate whether an applicant has complied with the written description requirement therefore requires an analysis of whether the skilled artisan would recognize, from the description provided, the applicants were in possession of sufficient compounds representing the full breadth of diversity of the genus claimed.

Here, applicants have claimed an extraordinarily large genus of chemical compounds, as evidenced by the multiple variable substituents provided on the core 2-phenyl benzimidazole compound, as well as the broad *Markush*-type groups describing the identity of a wide variety of chemical moieties which constitute the possible moieties for each variable substituent. Furthermore, within each of the delineated substituent groups, applicants have further indicated that each may further bear additional chemical moieties as substituents, giving rise to an exponentially larger group of possibilities for each of the distinctly named variables on the core compound. The size of the genus thus described is phenomenal, against which the applicants

have offered evidence of having made only 151 compounds falling within the genus as currently claimed. The particularly described compounds only represent a miniscule fraction of the genus which the applicants have claimed, and in no way either represent the breadth of variable moieties which applicants have claimed, nor permit the skilled artisan to recognize that such claim breadth was actually in the applicants possession as of the time of filing the instant application. This is particularly relevant in terms of the breadth of the Markush groups described for a number of variable substituents. This is of particular relevance to the variable substituents R6 and R1. Applicants have claimed in their broadest embodiments a variety of multiply substituted chemical moieties, but have only offered evidence that compounds featuring as R6 either methoxy or bromo substituents, and for R1 either 2-methoxy-, 2-thiomethyl-, or 2-dimethylamino-ethyl or lower alkyl moieties were actually made. Such disclosure cannot support the breadth of the claims as currently presented.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,855,714 (hereinafter "Blume"), in view of George Patani & Edmond LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, 96 CHEM. REV. 3147 (1996) (hereinafter "Patani").

Blume recites not only the genus of 2-aryl benzimidazoles additionally substituted on the 1 N and the 5-7 carbons of the benzimidazole ring, but also discloses a number of specifically recited compounds falling within the genus so described. (C.9, L.8 – C.10, L.65). While, following the guidance offered by *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994), such a disclosure cannot, without more, lead to the anticipation or obviousness of specifically claimed species or even a genus which differs in scope, Blume additionally describes a number of specific 2-phenyl benzimidazoles of particular interest to the instant application. Table 1, recited in columns 19-24 of the Blume patent, recites 113 specific 2-aryl benzimidazole compounds, including the *para*- substituted 2-phenyl benzimidazoles 32, 36, 40, 55, 58, 74, 84, and 86. (Table 1). The compounds referenced above have a common 1-(3-methoxypropyl) substitution, as well as either a methyl, trifluoromethyl, or t-butyl moiety substituted at the *para*-position of the phenyl substituent. (*Id.*). Furthermore, each of the above compounds carries on the 6-position of the benzimidazole ring a (5-(methoxycarbonyl)pentyl)oxy, (5-carboxy-pentyl)oxy, or (5-((3-methoxypropyl)amino-carbonyl)pentyl)oxy moiety. These substitutions correspond respectively to the lower alkyl substitution of R2, the lower alkoxy substitution of R1, and the substituted lower alkoxy substituents of R5. Blume additionally indicates the compounds

described can be compounded into pharmaceutically useful compositions by their mixture with pharmaceutically acceptable vehicles. (Claim 12).

Despite this correlation, the remaining benzimidazole carbons capable of bearing substituents in the Blume compounds bear only hydrogen atoms, compared to the requirement of the instant claims that substituents R3 and R6 cannot be hydrogen atoms, but instead can be, for example, halogen atoms.

Patani discloses a number of importan6t substitution patterns known to medicinal chemists which are commonly employed to modify known compounds having medicinal effects. (Patani, Pg. 3147). One of the most well known bioisosteric substitutions is that of a fluorine for a hydrogen atom. (Pg. 3149). With this understanding, it would have been prima facie obvious to a medicinal chemist aware of the teachings of Blume to replace any or all of the hydrogen atoms found on the 2-phenyl substituted benzimidazole compounds disclosed therein with fluorine atoms. This is because of the well-known bioisosteric equivalence of hydrogen and fluorine, well known to the skilled artisans at the time of the instant invention.
While sufficient to render obvious the compounds recited in Claims 1-3, some of the compounds recited in Claim 4 still differ slightly from the compounds resulting from the combination of Blume and Patani. However, when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. *In re Wilder*, 563 F.2d 457 (CCPA 1957). Stated alternatively, obviousness may be based solely upon structural similarity (an established structural relationship between a prior art compound and the claimed compound, as with homologs). *In re Duel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). The necessary motivation to make the claimed compound, and thus the *prima facie* case of obviousness, arises from the

reasonable expectation that compounds similar in structure will have similar properties. *In re Gyurik*, 596 F.2d 1012, 1018 (CCPA 1979). Furthermore, mere structural isomers of prior art compounds are unpatentable unless they possess some unexpected advantage or property not possessed by the prior art compound.

> "[N]ovel members of a homologous series of chemical compounds must possess some unobvious or unexpected beneficial properties not possessed by a homologous compound disclosed in the prior art." We stated that novelty alone, without invention, is not sufficient to lend patentability to a claim. . . . [C]hemists understand that members of a homologous series of chemical compounds possess the same principal characteristics which vary gradually from member to member, and that knowing the chemical and physical properties of one of the members suggests the properties of the other members." *In re Norris*, 179 F.2d 970, 84 USPQ 458 (CCPA 1950).

Against this backdrop, for example, 4-bromo-2-(4-isopropylphenyl)-7-methoxy-1-(2-methoxyethyl)-1H-benzoimidazole cannot be said to be an unobvious modification of, for example, the 2-(4-tert-butyl-phenyl)-6-[(5-carboxypentyl)oxy]-1-(3-methoxy-propyl)-benzimidazole, as the phenyl and 1 substituents differ from those in the claimed compounds by a single methylene group, and are therefore considered homologous substituents as are the methoxy of the instant claims and the 5-carboxypentyl)oxy of the Blume reference, and the 4-bromo substituent is a bioisosteric equivalent to the hydrogen of the Blume compound. The difference in positional substitution of the alkoxy benzimidazole substituents represents little more than a positional isomer of the prior art compound, and therefore absent evidence of unexpected results, cannot be considered patentable.

***Technological Background Material***

The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Patents 2,500,487, 3,080,282, 3,162,574, 3,294,542, 6,184,235, 6,696,437.

***Conclusion***

No Claims are currently allowable, however, applicants are strongly encouraged to contact the examiner to discuss responses that will identify and claim patentable subject mater. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean Basquill whose telephone number is (571) 270-5862. The examiner can normally be reached on Monday through Thursday, between 8AM and 6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean Basquill/
Examiner, Art Unit 1613

/Jeffrey S. Lundgren/
Primary Examiner, Art Unit 1639